PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)

May 19, 2009

NDA 22-275

SAMSCA™ (tolvaptan)

Vasopressin antagonist

Otsuka Pharmaceutical Development & Commercialization, Inc.

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Rockville, Maryland 20850

As authorized US Agent of Otsuka Pharmaceutical Company, Ltd., Tokyo, Japan

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PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I GOALS:

To mitigate the potential risk of osmotic demyelination syndrome (ODS) by:

- Educating healthcare providers (HCPs) on the risk of overly rapid correction of serum sodium associated with SAMSCA and the need for initiating SAMSCA in a hospital to ensure proper titration and monitoring
- Informing patients of the serious risk associated with the use of SAMSCA, particularly the risk of osmotic demyelination syndrome

II REMS Elements

A. Medication Guide

A Medication Guide will be dispensed with each SAMSCA prescription in accordance with 21 CFR 208.24. The Medication Guide will be included with each commercially packaged unit of use of SAMSCA. Cartons will include 10 tablets (i.e., 10 units of use) and 10 Medication Guides which equals one Medication Guide per unit of use. Please see appended Medication Guide.

B. Communication Plan

In accordance to FDCA 505-1(e)(3), Otsuka will implement a communication plan to healthcare providers (HCPs) who are involved in the prescribing, purchasing, dispensing or administration of SAMSCA for both inpatient and outpatient settings at time of launch, by conveying the following information:

- The requirement to initiate and re-intiate therapy in a hospital;
- The risks associated with overly-rapid correction of serum sodium;

- Reinforcement that a patient Medication Guide should be provided to patients with every prescription of SAMSCA.

This element of the REMS is not intended to continue over the lifetime of the product; it will function only to disseminate information about the risk of ODS associated with use of SAMSCA and measures to assure safe use.

The communication plan includes a Dear Healthcare Provider Letter and a Prescriber Brochure.

1. Dear Healthcare Provider Letter

Otsuka will issue a Dear Healthcare Provider Letter to targeted healthcare providers within 60 days of the REMS approval. The purpose of the letter is to inform healthcare providers of the risk of too rapid rise of serum sodium leading to osmotic demyelination syndrome and the requirement to initiate and re-initiate SAMSCA in a hospital setting to allow for appropriate monitoring of serum sodium.

Otsuka will disseminate the Dear Healthcare Provider Letters to target US healthcare providers in the following specialties: hospital- and community-based internal medicine specialists, cardiologists, endocrinologists, hepatologists, nephrologists, oncologists and hospital and retail pharmacists. The mailing will be re-distributed every 6 months for the first year, then annually for the following 2 years. Please see appended Dear Healthcare Provider Letter.

2. Healthcare Provider Education

Otsuka will provide a Prescriber Brochure to educate healthcare providers about the proper use, titration and monitoring of SAMSCA. Please see appended Prescriber Brochure.

The Prescriber Brochure will be included with the Dear Healthcare Provider Letter, and will be distributed as indicated above. In addition, both documents will be posted on the website, samsca.com. The brochure will also be presented and distributed by

Otsuka sales representatives. This effort will be supplemented by education by Medical Science Liaisons.

C. Elements for Safe Use

The REMS for SAMSCA does not include other elements to assure safe use other than the Medication Guide and the Communication Plan described above.

D. Implementation System

The REMS for SAMSCA does not include Elements to Assure Safe Use; therefore, an implementation system is not required.

E. Timetable for Submission of Assessments

REMS Assessments will be performed and submitted to FDA. The first REMS Assessment will evaluate the first 18 months following approval; the second REMS Assessment will evaluate the first 3 years from approval; the third REMS Assessment will evaluate the first 7 years from approval (see table below). The assessments are to be received by the FDA on the due dates. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment time interval.

Timetable for Assessment of the REMS

Assessment	Month/Year of Submission
1st REMS Assessment (18 months from approval)	November 2010
2nd REMS Assessment (3 years from approval)	May 2012
3rd REMS Assessment (7 years from approval)	May 2016

((Otsuka America Logo))

Dear Healthcare Provider,

SAMSCA™ (tolvaptan) is a new orally-administered selective vasopressin V_2-receptor antagonist.

SAMSCA is indicated for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure, cirrhosis, and syndrome of inappropriate antidiuretic hormone (SIADH).

Important Limitations

- Patients requiring intervention to raise serum sodium urgently to prevent or to treat serious neurological symptoms should not be treated with SAMSCA
- It has not been established that raising serum sodium with SAMSCA provides a symptomatic benefit to patients

WARNING: INITIATE AND RE-INITIATE IN A HOSPITAL AND MONITOR SERUM SODIUM

- SAMSCA should be initiated and re-initiated in patients only in a hospital where serum sodium can be monitored closely
- Too rapid correction of hyponatremia (e.g., >12 mEq/L/24 hours) can cause osmotic demyelination resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma and death. In susceptible patients, including those with severe malnutrition, alcoholism or advanced liver disease, slower rates of correction may be advisable.

Patients should be in a hospital for initiation and re-initiation of therapy, to evaluate the therapeutic response and because too rapid correction of hyponatremia can cause osmotic demyelination resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma, and death.

The usual starting dose for SAMSCA tablets is 15 mg administered once daily without regard to meals. Increase the dose to 30 mg once daily, after at least 24 hours, to a maximum of 60 mg once daily, as needed to achieve the desired level of serum sodium.

During initiation and titration, frequently monitor for changes in serum sodium. Avoid fluid restriction during the first 24 hours of therapy. Patients receiving SAMSCA should be advised that they can continue ingestion of fluid in response to thirst.

Too rapid correction of serum sodium can cause serious neurologic sequelae (see Boxed WARNING**):**

Osmotic demyelination syndrome is a risk associated with too rapid correction of hyponatremia (e.g., >12 mEq/L/24 hours). Osmotic demyelination results in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma or death. In susceptible patients, including those with severe malnutrition, alcoholism or advanced liver disease, slower rates of correction may be advisable. In controlled clinical trials in which tolvaptan was administered in titrated doses starting at 15 mg once daily, 7% of tolvaptan treated subjects with a serum sodium <130 mEq/L had an increase in serum sodium greater than 8 mEq/L at approximately 8 hours and 2% had an increase greater than 12 mEq/L at 24 hours. Approximately 1% of placebo-treated subjects with a serum sodium <130 mEq/L had a rise greater than 8 mEq/L at 8 hours and no patient had a rise greater than 12 mEq/L/24 hours. None of the patients in these studies had evidence of osmotic demyelination syndrome or related neurological sequelae, but such complications have been reported following too rapid correction of serum sodium.

Patients treated with SAMSCA (tolvaptan) should be monitored to assess serum sodium concentrations and neurologic status, especially during initiation and after titration. Subjects with SIADH or very low baseline serum sodium concentrations may be at greater risk for too rapid correction of serum sodium. In patients receiving SAMSCA who develop too rapid a rise in serum sodium, discontinue or interrupt treatment with SAMSCA and consider administration of hypotonic fluid. Fluid restriction during the first 24 hours of therapy with SAMSCA may increase the likelihood of overly-rapid correction of serum sodium, and should generally be avoided.

The most common adverse reactions (incidence ≥ 5% more than placebo) seen in two 30-day controlled clinical trials were thirst (tolvaptan=16%, placebo=5%), dry mouth (tolvaptan=13%, placebo=4%), asthenia (tolvaptan=9%, placebo=4%), constipation (tolvaptan=7%, placebo=2%), pollakiuria/polyuria (tolvaptan=11%, placebo=3%) and hyperglycemia (tolvaptan=6%, placebo=1%). In these trials, 10% (23/223) of tolvaptan-treated patients discontinued treatment because of an adverse event, compared to 12% (26/220) of placebo-treated patients; no adverse reaction resulting in discontinuation of trial medication occurred at an incidence of >1% in tolvaptan-treated patients.

Please see accompanying FULL PRESCRIBING INFORMATION, including **Boxed WARNING.**

SAMSCA is contraindicated in the following conditions:

- Urgent need to raise serum sodium acutely—SAMSCA has not been studied in a setting of urgent need to raise serum sodium acutely
- Inability of the patient to sense or appropriately respond to thirst
- Hypovolemic hyponatremia
- Concomitant use of strong CYP 3A inhibitors
- Anuric patients

Enclosed please find the Prescriber Brochure, which is intended to inform healthcare providers about the proper use, titration, and monitoring of SAMSCA. Also, with every prescription of SAMSCA, please be sure to provide your patients with the Medication Guide found in the drug package. This brochure will help them better understand the risks and benefits of SAMSCA.

If you need additional information about SAMSCA, please contact Otsuka Medical Affairs toll-free at 1-800-441-6763 (9 am to 5 pm ET, Monday through Friday), or visit **www.samsca.com**.

Sincerely,

Martin Rose, MD, JD
Vice President, Medical Affairs
Otsuka America Pharmaceutical, Inc.

SAMSCA™
(tolvaptan)
Prescriber Brochure

SAMSCA™ is indicated for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure, cirrhosis, and syndrome of inappropriate antidiuretic hormone (SIADH).

Important limitations

- Patients requiring intervention to raise serum sodium urgently to prevent or to treat serious neurological symptoms should not be treated with SAMSCA
- It has not been established that raising serum sodium with SAMSCA provides a symptomatic benefit to patients

WARNING: INITIATE AND RE-INITIATE IN A HOSPITAL AND MONITOR SERUM SODIUM

- SAMSCA should be initiated and re-initiated in patients only in a hospital where serum sodium can be monitored closely
- Too rapid correction of hyponatremia (e.g., >12 mEq/L/24 hours) can cause osmotic demyelination resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma and death. In susceptible patients, including those with severe malnutrition, alcoholism or advanced liver disease, slower rates of correction may be advisable.

Please see accompanying FULL PRESCRIBING INFORMATION, including Boxed WARNING.

SAMSCA™ (tolvaptan)
Prescriber Brochure

Please read this brochure for answers to your questions about SAMSCA—an orally administered selective vasopressin V2-receptor antagonist. The information provided is intended to inform healthcare providers about the proper use, titration, and monitoring of SAMSCA.

What is the indication for SAMSCA?
SAMSCA is indicated for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure, cirrhosis, and syndrome of inappropriate antidiuretic hormone (SIADH).

Important Limitations
- Patients requiring intervention to raise serum sodium urgently to prevent or to treat serious neurological symptoms should not be treated with SAMSCA
- It has not been established that raising serum sodium with SAMSCA provides a symptomatic benefit to patients

What is the dosing regimen for SAMSCA?
- SAMSCA should be initiated and re-initiated only in a hospital where serum sodium can be monitored closely
- The starting dose for SAMSCA tablets is 15 mg administered once daily without regard to meals
- After a minimum of 24 hours, the dose can be increased to 30 mg once daily to a maximum of 60 mg (two 30-mg tablets) once daily, as needed to achieve the desired level of serum sodium
- During initiation and titration, frequent monitoring is advised for changes in serum electrolytes and volume

Dosage forms and strengths
15 mg, 30 mg, 60 mg

Is there a need to adjust dosage for special populations?
There is no need to adjust dose based on age, gender, or race; cardiac, hepatic, or renal function.

Why is SAMSCA initiated and re-initiated in a hospital?
Patients should be in a hospital for initiation or re-initiation of therapy to evaluate the therapeutic response and monitor serum sodium concentrations. Too rapid correction of hyponatremia can cause osmotic demyelination resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma and death.

Please see accompanying FULL PRESCRIBING INFORMATION, including Boxed WARNING.

SAMSCA™ (tolvaptan)
Prescriber Brochure

What is the risk of overly rapid correction of serum sodium?

- Too rapid correction of hyponatremia (e.g., >12 mEq/L/24 hours) can cause osmotic demyelination syndrome (ODS) resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma, or death. In susceptible patients, including those with severe malnutrition, alcoholism or advanced liver disease, slower rates of correction may be advisable.
- Such sequelae may develop over a course of one to several days following overly-rapid correction of hyponatremia[1]

Who is at risk for ODS?

Anyone who undergoes a rapid rise in serum sodium is at risk.[2] However, the risk for ODS is greater if the serum sodium was low for at least 2 days before correction.[2] In addition, patients with severe chronic hyponatremia have an increased risk of ODS.[3]

- Patients may be more at risk for ODS if they have cirrhosis, are malnourished, have low serum sodium concentration, or are chronic alcoholics
- Subjects with SIADH or very low baseline serum sodium concentrations may be at greater risk for too rapid correction of serum sodium

Monitoring serum sodium conditions

- Patients treated with SAMSCA should be monitored to assess serum sodium concentrations and neurologic status, especially during initiation and after titration.
    - In controlled clinical trials in which tolvaptan was administered in titrated doses starting at 15 mg once daily, 7% of tolvaptan-treated subjects with a serum sodium < 130 mEq/L had an increase in serum sodium greater than 8 mEq/L at approximately 8 hours and 2% had an increase greater than 12 mEq/L at 24 hours. Approximately 1% of placebo-treated subjects with a serum sodium < 130 mEq/L had a rise greater than 8 mEq/L at 8 hours and no patient had a rise greater than 12 mEq/L/24 hours.
    - None of the patients in these studies had evidence of osmotic demyelination syndrome or related neurological sequelae, but such complications have been reported following too-rapid correction of serum sodium.
- In patients receiving SAMSCA who develop too rapid a rise in serum sodium, discontinue or interrupt treatment with SAMSCA and consider administration of hypotonic fluid.

Please see accompanying FULL PRESCRIBING INFORMATION, including Boxed WARNING.

SAMSCA™ (tolvaptan)
Prescriber Brochure

What are the contraindications for SAMSCA?
SAMSCA is contraindicated in the following conditions:

- **Urgent need to raise serum sodium acutely**. SAMSCA has not been studied in a setting of urgent need to raise serum sodium acutely
- **Inability of the patient to sense or appropriately respond to thirst**. Patients who are unable to auto-regulate fluid balance are at substantially increased risk of an overly-rapid correction of serum sodium, hypernatremia, and hypovolemia
- **Hypovolemic hyponatremia**. Risks associated with worsening hypovolemia, including complications such as hypotension and renal failure, outweigh possible benefits
- **Concomitant use of strong CYP 3A inhibitors**. Ketoconazole 200 mg administered with SAMSCA increased SAMSCA exposure by 5-fold. Larger doses would be expected to produce larger increases in SAMSCA exposure. There is not adequate experience to define the dose adjustment that would be needed to allow safe use of SAMSCA with strong CYP 3A inhibitors such as clarithromycin, ketoconazole, itraconazole, ritonavir, indinavir, nelfinavir, saquinavir, nefazodone, and telithromycin
- **Anuric patients.** In patients unable to produce urine, no clinical benefit can be expected

Should SAMSCA be used in cirrhotic patients with hyponatremia?
SAMSCA should be used in cirrhotic patients only when the need to treat outweighs the risk of gastrointestinal bleeding. In patients with cirrhosis treated with SAMSCA in hyponatremia trials, gastrointestinal bleeding was reported in 6 out of 63 (10%) SAMSCA-treated patients and 1 out of 57 (2%) placebo-treated patients.

Importance of Fluids

- SAMSCA therapy induces copious aquaresis, which is normally partially offset by fluid intake. For this reason, patients given SAMSCA should have access to water. Dehydration and hypovolemia can occur, especially in potentially volume-depleted patients receiving diuretics or those who are fluid restricted.
- Fluid restriction during the first 24 hours of therapy with SAMSCA may increase the likelihood of overly-rapid correction of serum sodium, and should generally be avoided
- After 24 hours use your clinical judgment
- In multiple-dose, placebo-controlled trials in which 607 hyponatremic patients were treated with SAMSCA, the incidence of dehydration was 3.3% for SAMSCA and 1.5% for placebo-treated patients

What should patients know about the risk of dehydration?
Patients should be advised about the risk of dehydration:

- SAMSCA is contraindicated in patients who are unable to sense or respond appropriately to thirst
- To avoid dehydration, patients must have water available at all times and to continue ingestion of fluid in response to thirst. Do not give to patients who don't have access to water
- Patients should also inform their healthcare providers if they develop conditions that increase the risk of dehydration, such as diarrhea or vomiting, and cannot drink normally

Please see accompanying FULL PRESCRIBING INFORMATION, including Boxed WARNING.

Can SAMSCA be coadministered with hypertonic saline?

- There is no experience with concomitant use of SAMSCA and hypertonic saline
- Concomitant use with hypertonic saline is not recommended

What other drugs affect exposure to tolvaptan?

CYP 3A Inhibitors
Tolvaptan is metabolized by CYP 3A. CYP 3A inhibitors can lead to a marked increase in tolvaptan concentrations. Do not use SAMSCA with strong inhibitors of CYP 3A and avoid concomitant use with moderate CYP 3A inhibitors.

CYP 3A Inducers
Avoid co-administration of CYP 3A inducers (e.g., rifampin, rifabutin, rifapentin, barbiturates, phenytoin, carbamazepine, St. John's Wort) with SAMSCA, as this can lead to a reduction in the plasma concentration of tolvaptan and decreased effectiveness of SAMSCA treatment. If co-administered with CYP 3A inducers, the dose of SAMSCA may need to be increased.

P-gp Inhibitors
The dose of SAMSCA may have to be reduced when SAMSCA is co-administered with P-gp inhibitors, e.g., cyclosporine.

Can SAMSCA be used in patients who are pregnant or who are breast-feeding?
SAMSCA is a Pregnancy Category C therapy. There are no adequate and well-controlled studies of SAMSCA use in pregnant women. SAMSCA use should be avoided during pregnancy unless the potential benefit justifies the potential risk to the fetus.

It is not known whether SAMSCA is excreted into human milk. SAMSCA is excreted into the milk of lactating rats. Because many drugs are excreted into human milk and because of the potential for serious adverse reactions in nursing infants from SAMSCA, a decision should be made to discontinue nursing or avoid SAMSCA, taking into consideration the importance of SAMSCA to the mother.

To lessen your patients' risk of ODS while taking SAMSCA, make sure to tell them the following:

- Treatment should be started and re-started only in the hospital, where the sodium levels in their blood can be monitored closely
- Not to take SAMSCA if they can't tell if they are thirsty
- To prevent dehydration while taking SAMSCA, they should drink when they are thirsty and have water available to drink at all times, unless the healthcare provider tells them otherwise
- Not to stop and restart SAMSCA on their own
- If they stop SAMSCA for any reason, they should talk to their healthcare provider right away

Other important information your patients should know:

- Patients should be advised to call their healthcare provider immediately if they experience any side effects that bother them while taking SAMSCA
- Patients should read the Medication Guide to understand the risks and benefits of SAMSCA

Please see accompanying FULL PRESCRIBING INFORMATION, including Boxed WARNING.

SAMSCA™ (tolvaptan)
Prescriber Brochure

Please provide patients with the Medication Guide with every prescription of SAMSCA. This guide will help your patients better understand the risks and benefits of SAMSCA.

For more information, please visit www.samsca.com.

References: 1. Verbalis JG, Goldsmith SR, Greenberg A, Schrier RW, Sterns RH. Hyponatremia treatment guidelines 2007: expert panel recommendations. *Am J Med.* 2007;120(suppl 11A):S1-S21. **2.** National Institutes of Health. NINDS central pontine myelinolysis information page. http://www.ninds.nih.gov/disorders/central_pontine/central_pontine_myelinolysis.htm. Accessed February 24, 2009. **3.** Douglas I. Hyponatremia: why it matters, how it presents, how we can manage it. *Cleve Clin J Med*. 2006;73(suppl 3):S4-S12. **4.** Adrogué HJ. Consequences of inadequate management of hyponatremia. *Am J Nephrol*. 2005;25(3):240-249.

Please see accompanying FULL PRESCRIBING INFORMATION, including Boxed WARNING.

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